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#133
IDP

Attorney Docket No. 02022097 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

Sapse, Alfred T.

Application No. 09/234,532

Filed: January 21, 1999

For: COMPOSITIONS OF ANTI-HIV AND ANTI-CORTISOL COMPOUNDS AND METHODS FOR DECREASING THE SIDE EFFECTS OF ANIT-HIV DRUGS IN A HUMAN

Group Art Unit 1643

Examiner: H. OWENS, JR.

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Timothy Hubalik

SUPPLEMENTAL DECLARATION OF DR. VASSILIOS PAPADOPOULOS UNDER 37 C.F.R. §1.132 IN SUPPORT OF PATENTABILITY

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I, Dr. Vassilios Papadopoulos, being duly cautioned declare as follows:

1. I am a professor of cell biology, pharmacology and neuroscience in the department of Pharmacology & Neurosciences at Georgetown University Medical Center.

2. I have been a professor at Georgetown University Medical Center since 1988.

3. I previously submitted a §132 Declaration supporting the patentability of the invention disclosed in this application on September 18, 2000.

4. In the Declaration, I discussed the results of a study conducted at Georgetown University Medical Center and released in May 2000. The results showed that a

combination of procaine, zinc sulfate heptahydrate and ascorbic acid has a cortisol inhibition effect that is more elevated than the coritsol inhibition effect of each ingredient administered separately (a synergistic effect). The combination of procaine, zinc sulfate heptahydrate and ascorbic acid led to a clear and extremely significant cortisol inhibition.

5. In the September 18, 2000 Declaration, I did not include the actual data from this study.

6. The results obtained from this study are attached as Exhibit A.

7. All statements made of my own knowledge are true and all statements made on information and belief are believed to be true.

8. I have been warned that willful false statements and the like are punishable by fine or imprisonment, or both (18 U.S.C. 1001) and may jeopardize the validity of the application or any patent issuing thereon.

_____ _____

Date Dr. Vasillios Papadopoulos

EXHIBIT A

4.0 GENERAL INVESTIGATIONAL PLAN FOR THE NEXT YEAR

During the course of the next year, both nonclinical and clinical investigations will occur in parallel.

4.1 NONCLINICAL STUDIES

As the posited basis of ANTICORT's mechanism of action is inhibition of cortisol biosynthesis, nonclinical *in vitro* assessments of cortisol biosynthesis inhibition will be performed by Dr. Vassilios Papadopoulos at Georgetown University.

Papadopoulos and associates have examined the effect of ANTICORT and its components on corticosteroid synthesis in a human cell tissue culture system. Adrenocorticotrophic hormone responsive human adrenal cells (H-295R) were pre-exposed to varying concentrations of ANTICORT, procaine HCl, ascorbic acid, and zinc sulfate heptahydrate. After a 48 hour incubation, the growth medium was removed and fresh medium containing 1 mmol/L $(Bu)_2$-cAMP was added to stimulate cortisol biosynthesis. This induction resulted in a 3- to 4-fold increase in cortisol production. Cells were then incubated an additional 48 hours in the presence of varying concentrations of ANTICORT or its components. Control cultures were included that did not contain the inducer, $(Bu)_2$-cAMP. At the end of the treatment period, cortisol levels in the culture media were measured by radioimmunoassay. The results of these experiments are shown in Figure 1.

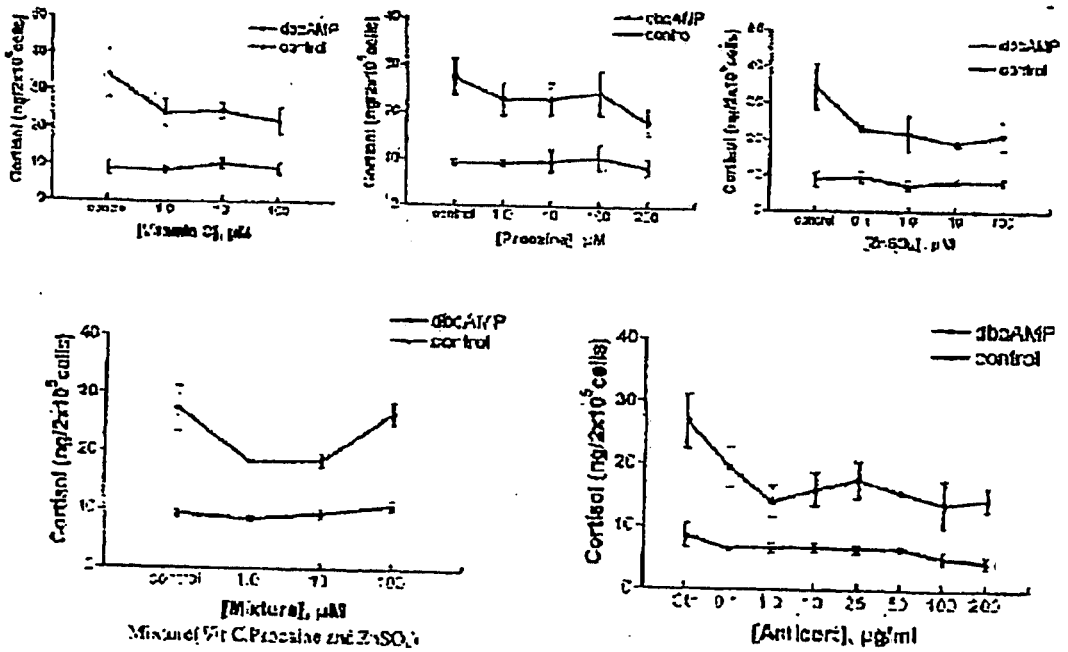

Figure 1. *In Vitro* **Effect of ANTICORT and ANTICORT Components on Cortisol Biosynthesis.**

ANTICORT inhibited cAMP-stimulated cortisol production, in a dose-dependent fashion, over a concentration range of 0.1 to 200 µg/mL ($p < 0.001$). At 1.0 µg/mL, ANTICORT inhibited cortisol biosynthesis by approximately 54% compared to control cell values. Procaine HCl inhibited cortisol biosynthesis in a statistically significant manner only at a concentration of 200 µmol/L. Interestingly, a 1:1:1 ratio of ascorbic acid, procaine HCl, and zinc sulfate heptahydrate induced a biphasic response in which an initial inhibition of cortisol biosynthesis (approximately 36% at 1.0 µmol/mL) was followed by a rebound effect (no inhibition) at 100 µmol/L. In addition, pH changes in the order of 0.5 units significantly affected the solubility of the zinc component of ANTICORT. This observation, coupled with the biphasic cortisol-inhibition profile of the ascorbic acid/procaine/zinc sulfate mixture, may indicate that a pH-dependent procaine/zinc complex may be responsible for the observed anti-steroidogenesis activity of ANTICORT (V. Papadopoulos, personal communication). Experiments are currently in progress to determine whether such a biologically active complex exists and, if it does, to further characterize it.

4.2 CLINICAL STUDIES

A Phase 1 clinical protocol (SII-102PK) is planned. The proposed study is a double-blind, placebo-controlled, single-dose, dose-escalating crossover study designed to confirm that ANTICORT inhibits cortisol production in normal volunteers. This study will consist of a Screening Period (14 days), Treatment Period (24 days), and a Follow up Period (1 day). Four dose levels (200, 400, 600, and 800 mg) of ANTICORT will be administered during the Treatment Period. Sixteen subjects will be enrolled in this study and randomized to receive placebo and 3 of the 4 doses (200, 400, 600 and 800 mg ANTICORT) administered. Each dose level will include a ratio of 12 subjects receiving active drug to 4 receiving placebo. All subjects who complete at least one ANTICORT dose level will be included in the procaine and cortisol pharmacokinetic analysis. All subjects will be included in the safety analysis. As there have been only 1 adverse event and no serious adverse events reported in the ongoing study, SII-101PK, it is unlikely that the proposed study poses significant risk to participants.